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Hyperleucocytosis and Leucostasis in Acute Myeloid Leukaemia: A Challenging Clinical Situation

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ABSTRACT

Hyperleucocytosis is defined as a white cell count (WBC) >50x10^9/L or commonly 100x10^9/L in a patient with leukaemia. Hyperleucocytosis with leucostasis is most often seen in patients with Acute Myeloid leukaemia (AML). AML with hyperleucocytosis is thought to have a poor prognosis because of a higher risk of early death due to complications such as disseminated intravascular coagulation (DIC), tumour lysis syndrome (TLS), and leucostasis, as well as a higher likelihood of long-term relapse. Leucostasis is considered a medical emergency since it has the potential to cause ischemia in vital organs with high mortality requiring immediate intervention. The molecular mechanisms behind hyperleucocytosis remain poorly understood.

Key words: acute myeloid leukaemia, AML, hyperleucocytosis, leucostasis, tumour lysis syndrome, disseminated intravascular coagulation, DIC.

Introduction

AML is the most common type of leukaemia in adults.[1] About 5% to 20% of newly diagnosed acute myeloid leukaemia (AML) patients present with hyperleucocytosis.[2-12] Hyperleucocytosis is also seen with Acute Lymphoblastic leukaemia, Chronic Lymphocytic leukaemia, and Chronic Myeloid leukaemia, but it is rarely associated with leucostasis. Hyperleucocytosis increases the risk for the development of tumour lysis syndrome (TLS), disseminated intravascular coagulation (DIC), and leucostasis, which can occur in up to 30%, 30%, and 45% of patients, respectively. Leucostasis is a medical emergency which can occur due to obstruction of small blood vessels by malignant blast cells resulting in tissue and organ ischemia with high potential for mortality and morbidity. The mortality from leucostasis in acute leukaemia reaches about 40%, which usually occurs within a few weeks of diagnosis.[13]

The pathophysiology of leucostasis is not clear. Leucostasis in AML is due to various factors. Increased blood viscosity due to large Leukaemic blasts which are less deformable than normal blood cells cause mechanical obstruction of small blood vessels leading to hypoperfusion and ischemic damage in organs. Leukaemic blasts produce

cytokines (TNF-α or IL-1β), that induce the expression of cell adhesion molecules (i.e. selectins and VCAM-1) on endothelial cells, leading to blast cell recruitment and adhesion to vascular endothelium.[14,15] Leukaemic blasts also release matrix metalloproteinases (MMP) that lead to vascular wall disruption, perivascular tissue infiltration, and microhaemorrhages.[16-18] The central CNS and lungs are the major affected end organs, but cardiac, gastrointestinal, renal and other organ systems may be affected. Pulmonary manifestations of leucostasis include dyspnoea, tachypnoea, hypoxia, diffuse alveolar haemorrhage, and respiratory failure, while CNS complications include confusion, lethargy, dizziness, headache, somnolence, tinnitus, intraparenchymal bleeding, and coma.

Leucostasis is typically diagnosed on the basis of clinical manifestations associated with organ ischemia in patients with hyperleucocytosis, after excluding other possible causes.[13,19] Patients suspected of having leucostasis are often given a series of diagnostic tests such as chest X-ray, blood cultures, brain imaging, cerebrospinal fluid analysis, liver enzymes, lactate dehydrogenase, and peripheral blood morphology.

The incidence of hyperleucocytosis and leucostasis differs among various subtypes of leukaemia. Among the French-American-British (FAB) classification of AML, monocytic and myelomonocytic AML (M4 and M5) and the microgranular subtypes (M3v) of acute promyelocytic leukaemia (APL) have been associated with hyperleucocytosis.[4,20,21] Certain cytogenetic and molecular abnormalities like diploid karyotype and patients with FLT3 mutations, NPM1 mutation, CEBPA mutation and KMT2A (MLL) abnormalities on chromosome 11q23 are frequently found in AML with hyperleucocytosis.[22-27] However, the mechanisms by which these mutations lead to hyperleucocytosis remain poorly understood.

TLS and DIC:

Patients with hyperleucocytosis may develop concurrent TLS and DIC. TLS is characterized by hyperuricaemia, hyperphosphataemia, hypocalcaemia, and hyperkalaemia because of the rapid destruction of tumour cells which can be complicated by renal failure due to urate crystal deposition in the kidneys and cardiac arrhythmias. Treatment of TLS needs supportive management of electrolytes, intravenous fluids to maintain urine output, and allopurinol or rasburicase to reduce the production of uric acid.

Disseminated intravascular coagulation (DIC) occurs in 30% to 40% of hyperleucocytic AML.[28] Leukaemic and endothelial cells may release tissue factors as a result of cell lysis, which would interfere with normal coagulation. When low levels of platelets and fibrinogen are combined with the consumption and depletion of clotting components, DIC results. Coagulopathy occurs when prothrombin time and activated partial thromboplastin time are prolonged, and D-dimer is elevated. DIC can be managed with transfusion of platelets, fibrinogen, and fresh frozen plasma (FFP). Coagulopathy is usually corrected when treating the underlying condition.

Management of hyperleucocytosis and leucostasis:

The management of the hyperleucocytosis with leucostasis includes intensive supportive care, interventions for rapid cytoreduction. Intravenous hydration, alkalization, allopurinol, or urate oxidase should begin immediately. Cytoreduction can be achieved either by mechanical removal of WBC with leukapheresis or immediate initiation of intensive chemotherapy or hydroxyurea, but the best mode of cytoreduction is still a matter of debate.[13,29] Cytoreductive treatment should start immediately at diagnosis of hyperleucocytic AML and must not be delayed or postponed by the leukapheresis procedure.

bridging strategy in patients where the haematologic malignancy is not yet diagnosed or where there is contraindication to induction chemotherapy.[30-32] The European Leukaemia Net (ELN) recommend considering hydroxyurea for patients not suitable for intensive chemotherapy. Hydroxyurea (50-60 mg/kg/day) is widely used to decrease WBC below 25×10^9/L, especially before starting HMA or venetoclax-based therapies.[33]

Leukapheresis:

It is defined as removal of white blood cells from the blood by the apheresis machine through centrifugation. During a single leukaphaeresis, the WBC count can be reduced by 10% to 70%.[34] The major limitation of leukapheresis is that the procedure does not remove blast cells from bone marrow. The residual blast cells in bone marrow may cause a transient rebound of hyperleucocytosis. Leukapheresis should be used in patients with symptoms of leucostasis provided there is no contraindication (cardiovascular comorbidities, haemodynamic instability, or coagulation disorders). In the 2019 consensus guidelines from the American Society for Apheresis, leukaphaeresis is considered a category II recommendation (acceptable second-line therapy) for patients with symptomatic hyperleucocytosis (i.e. leucostasis) and a category III (role not established) recommendation in cases of asymptomatic hyperleucocytosis.[35]

Current evidence on the use of leukapheresis for AML:

Currently, there are no randomized prospective studies that evaluated the survival benefit of leukapheresis in AML patients with leucostasis. A systematic review and meta-analysis of 13 studies with 1743 on hyperleucocytosis and AML showed no difference in short-term survival between patients who received leukapheresis plus chemotherapy versus chemotherapy alone.[36] There was no difference in early mortality between leukapheresis plus chemotherapy and chemotherapy alone, which comprised 486 patients who had leukapheresis and 1257 patients who did not. Another retrospective analysis of 779 patients with AML and white blood cell (WBC) >50 x 10^9/L reported no difference in outcomes between 113 patients who underwent leukapheresis and 666 patients who did not; clinical leucostasis was reported in one-quarter of the patients.[37] Use of leukapheresis had no impact on 30-day mortality, complete remission, or longer-term overall survival, according to multivariate analysis. Prophylactic leukaphaeresis has no benefits over intensive induction chemotherapy and supportive care.[38,39] Leukapheresis is not indicated in APL because it can aggravate coagulopathy and increase the risk of complications.[40] Other studies have revealed varying effects of leukapheresis on outcomes in AML with hyperleucocytosis, but there is no clear evidence that it reduced mortality.[20,28,38,41-45]

Induction chemotherapy:

Initial induction therapy selection depends on clinical features such as age, cytogenetics, comorbidities, and performance status. Prompt initiation of intensive induction therapy is suggested rather than treatment with single-agent therapy like hydroxyurea. Intensive treatment with DA (3+7) is still the gold standard approach for patients younger than 60 years without comorbid conditions. Patients older than 60 years or those with poor performance status or significant comorbidities are candidates for induction therapy with a lower-intensity agent (e.g. decitabine, azacitidine) combined with oral therapy (e.g. venetoclax). Addition of specific targeted drugs (e.g. Sorafenib/Midostaurin in FLT3 mutation) along with

suspected. After APL confirmation, idarubicin or arsenic trioxide should be added for proper cytoreduction treatment.[12] Intensive induction therapy significantly reduces the WBC count within 24 hours and is the fastest and most effective way to control hyperleucocytosis and associated end-organ effects.

Steroid:

Dexamethasone to conventional chemotherapy have found to be beneficial in patients with AML FAB-M5 having end organ damage (acute lung injury) and in the management of hyperleucocytosis.[46]

Cyclophosphamide:

A retrospective analysis has revealed that a single-dose intravenous high-dose cyclophosphamide (HDCy) 60 mg/kg over a four-hour period may be an effective means of cytoreduction in patients with hyperleucocytosis, with sustained reductions in WBC count noted in 75% of evaluable patients.[47]

Conclusion:

Hyperleucocytosis in AML may evoke an emergency clinical situation especially when it causes leucostasis, TLS and DIC. Cytoreduction with intensive chemotherapy, leukapheresis, and/or hydroxyurea as well as excellent supportive care of TLS and DIC remain the mainstay of therapy. However, management with these conventional strategies may often be challenging. Therefore, novel therapies are required to inhibit the mediators of vascular endothelial-myeloblast adherence (e.g. selectins, vascular cell adhesion molecule-1, intracellular adhesion molecule-1), endothelial activation (e.g. tumour necrosis factor-α or interleukin-1β), and soft tissue infiltration (e.g. metalloproteinase) for smooth management of hyperleucocytosis in AML.

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